memorandum to:

Dr. Graham Robertson
Melbourne

September 12, 1957

Comment on BARNES pedigree

(Ref. Sorsby, Clinical Genetics, pp. 303-306)

1. A number of clinical and genetic entities are grouped as hereditary ataxias. Without further etiological information, they cannot be sorted out. In this group, some pedigrees show recessive inheritance, others dominant, still others sex-linked. A limited incidence like this offers very little to go on for predictive purposes. However sex-linkage is clearly out of the question. The plausible genetic hypotheses are:

A. Recessive inheritance. In this case, both parents are heterozygous, Aa. (About 10% of the families showing the ataxias stem from cousin marriages; the hypothesis would be somewhat reinforced if this marriage were consanguineous, as appears not to be the case.) The a priori risk for each child is then ¼, which is statistically compatible with the observed 2/4 or ½, considering that families of similar genotype whose incidence is 0 or even perhaps 1 would be overlooked. The unaffected childrenwill also be heterozygous, and suffer the same risk that the parents have in mating with another heterozygote. Except for consanguinity, this risk is very small, though it did happen this time.

To recapitulate, this hypothesis predicts that ¼ of further children will be affected. Two-thirds of unaffected children will be heterozygous. In common with other matings of either parent, the matings of these children suffer a risk of 1% or less that the ataxia will recur, affecting 1/4 of the family. The remaining 99% or more of such matings would show no such recurrence, but would transmit the same 'risk' to their offspring. One third of unaffected children are homozygous AA, and produce exclusively normal gametes in this respect.

B. Dominant inheritance, either with irregular manifestation or following mutation in either parent. In this case, the a priori risk for further offspring is about ½, the unaffected children being normal homozygous AA. It is impossible to sta-

of affected offspring in other matings, while the other is 'safe'.

My purely intuitive predilections are for hypothesis A), but there is no certainty that either A or B holds. In experimental animals, these suppositions could be tested, and further, for a few diseases in man (e.g. sickle cell anemia) present knowledge suffices for unambiguous prediction. For most conditions, however, the state of human genetic knowledge assures the validity of statistical statements, but not of individual ones.

I trust these comments will be of some use in your own evaluation of the case. Please make whatever use you wish of them, within the realm of scientific comment, The interpretation of them to the patient should be the responsibility of his medical counselor, and I would recommend that they not be simply forwarded unless they are understood by the latter.

Yours sincerely,

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